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Session 4: CVD, diabetes and cancer - Evidence for the use of the Mediterranean diet in patients with CHD

McKeown, P., Logan, K., McKinley, M., Young, I., & Woodside, J. (2010). Session 4: CVD, diabetes and cancer - Evidence for the use of the Mediterranean diet in patients with CHD. *Proceedings of the Nutrition Society*, 69(1), 45-60. <https://doi.org/10.1017/S0029665109991856>

Published in:
Proceedings of the Nutrition Society

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
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Evidence for the use of the Mediterranean diet in patients with coronary heart disease

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1 **Abstract**

2 Diet is associated with the development of coronary heart disease (CHD). The incidence of CHD is
3 lower in Southern European countries than in Northern European countries and it has been proposed
4 that this difference may be due to diet. The traditional Mediterranean diet emphasises a high intake
5 of fruits, vegetables, bread, other forms of cereals, potatoes, beans, nuts, and seeds. It includes olive
6 oil as a major fat source and dairy products, fish, and poultry are consumed in low to moderate
7 amounts. Many observational studies have shown that the Mediterranean diet is associated with
8 reduced risk of CHD, and this has been confirmed by meta-analysis, while a single randomised
9 controlled trial, the Lyon Diet Heart study, showed a reduction in CHD risk in those following the
10 Mediterranean diet in the secondary prevention setting. However, it is uncertain whether the
11 benefits of the Mediterranean diet are transferable to other non-Mediterranean populations, and
12 whether the effects of the Mediterranean diet will still be feasible in light of the changes in
13 pharmacological therapy seen in CHD patients since the Lyon Diet Heart study was conducted.
14 Further randomised controlled trials are required, and if the risk-reducing effect is confirmed, then
15 the best methods to effectively deliver this public health message worldwide considered.

16

1 **Introduction**

2

3 The World Health Organisation has reported that, on a global scale in the period up to 2030, there
4 will be a dramatic shift in the distribution of deaths from younger to older people and from
5 communicable to non-communicable diseases, with the leading causes of death likely to be
6 coronary heart disease (CHD), cerebrovascular disease, HIV infection and COPD⁽¹⁾. Most of these
7 diseases are complex, reflecting the interaction between genetic and environmental influences,
8 including diet and physical activity.

9

10 Cardiovascular disease (CVD), which includes CHD, cerebrovascular disease and peripheral
11 vascular disease, is still the leading cause of death in the UK, being responsible for 35% of all
12 deaths⁽²⁾. Therefore, both the management and prevention of CVD are major public health issues in
13 the UK. Although mortality from CHD in the UK has been falling in the last four decades⁽²⁾, it
14 remains the major cause of premature death (before 75 years) in most affluent societies⁽³⁾.

15

16 **Coronary heart disease**

17 The major underlying disease process leading to CHD is atherosclerosis: a chronic inflammatory
18 disease⁽⁴⁾, which starts in early life and has stable and unstable phases⁽⁵⁾. Patients with the disease
19 may be asymptomatic, have symptoms of chest pain, or may present with sudden cardiac death. The
20 transition from a stable to an unstable phase results from the rupture of an atherosclerotic plaque
21 with associated partial or complete thrombosis of the artery⁽⁶⁾ (Figure 1). Typically, the patient then
22 presents with increasing symptoms leading to the development of an acute coronary
23 syndrome/myocardial infarction^(5,7). The diagnosis is based on clinical history and the results of
24 various investigations, including electrocardiography, exercise stress testing, imaging of the
25 coronary arteries and measurement of cardiac biomarkers.

26

27 **Risk factors for CHD**

28 The non-modifiable risk factors for CHD include genetic predisposition, gender, and age^(8,9).
29 However, the majority of risk factors which contribute to CHD risk, including dyslipidaemia,
30 hypertension, smoking, and diabetes, are modifiable⁽¹⁰⁾. Diet is also thought to be a major factor in
31 the development of CHD⁽¹¹⁾. An association between the risk of developing CHD and obesity has
32 been reported⁽¹⁰⁾, while rates of overweight and obesity are increasing⁽¹²⁾ and are high in patients
33 with CHD⁽¹³⁾. However, the relationship between obesity and CHD is complex, in that obesity is
34 known to increase the risk of developing type 2 diabetes, dyslipidaemia and hypertension⁽¹⁴⁾, all of
35 which are risk factors for CHD.

Diet and CHD

Lifestyle modifications (including diet) form part of strategies to prevent and delay the progression of CHD⁽¹⁵⁾. The development of CHD has traditionally been related to an increased consumption of cholesterol and saturated fat with low intakes of polyunsaturated fat⁽¹⁶⁾ and possibly also a suboptimal intake of micronutrients⁽¹⁷⁾. However, the results of cohort studies and randomised controlled trials (RCTs) have not been in agreement, for example for vitamin E and β -carotene⁽¹⁷⁾. A recent systematic review of the evidence supporting a causal link between dietary factors and CHD concludes that current evidence only supports a valid association of a limited number of dietary factors, including vegetable, nut and MUFA intake (negative association) and trans-fatty acid and high glycaemic index or load foods (positive association) with CHD⁽¹⁸⁾.

Assessment of whole dietary patterns versus single nutrients

The classical approach to assessing the relationship between diet and disease has been to focus on single nutrients or food items^(19,20). However, this approach often does not take into account the potential interactions between combinations of food items in a whole diet⁽²¹⁾. There is now much interest in analysing whole dietary patterns in relation to disease risk^(19,22,23), and some of these patterns were considered by Mente et al.⁽¹⁸⁾ in their systematic review. It has been suggested that the relationship between diet and CVD is likely to be multifaceted, involving a wide variety of dietary constituents, rather than individual nutrients⁽²⁴⁾. It is thought that an optimal diet for cardiovascular health is likely to have an extensive overlap with the traditional Mediterranean diet⁽²⁵⁾. In an overview of research on the Mediterranean diet, Willett⁽²⁶⁾ states that over 80% of CHD could be avoided by healthy food choices that are consistent with the traditional Mediterranean diet.

THE MEDITERRANEAN DIET

CHD has, traditionally, a low incidence in the Mediterranean region of Europe, leading to a higher life expectancy in these areas, when compared to Northern European countries⁽²⁰⁾. The benefits of the Mediterranean diet were first highlighted by Keys in the Seven Countries Study⁽²⁷⁾ and the MONICA Project confirmed a North-South gradient in Europe in the incidence of CHD⁽²⁸⁾. This was supported by the PRIME study, a cohort study of 10,000 men from Belfast and France, where a higher incidence of angina pectoris, MI and cardiac death was noted in Belfast compared to France⁽²⁹⁾. The lower incidence of CVD in the Mediterranean region of Europe is thought to be, at least partly, due to diet^(20,30).

Definition of the Mediterranean diet

Defining the Mediterranean diet is difficult, given the broad geographical area that covers the Mediterranean region. There are cultural, ethnic, religious, economic and agricultural production differences that result in different dietary practices in these areas^(15,31). For example, the fat content of the Mediterranean diet varies between the countries, being higher in Greece and lower in Spain⁽³²⁾.

However, the diet has been described as a pattern that emphasises a high intake of fruits, vegetables, bread, other forms of cereals, potatoes, beans, nuts, and seeds. It includes olive oil as a major fat source and dairy products, fish, and poultry are consumed in low to moderate amounts; eggs consumed zero to four times weekly; and little red meat consumed. In addition, wine is consumed in low to moderate amounts⁽¹⁵⁾. The key features of the dietary pattern have been expressed in the form of a diet pyramid (Figure 2).

Panagiotakos et al.⁽³³⁾ have described the Mediterranean diet in more detail as a dietary pattern implying: (a) daily consumption of unrefined cereals and cereal products, vegetables (2-3 servings/day), fruits (4-6 servings/day), olive oil (as the main added lipid), and non-fat or low-fat dairy products (1-2 servings/day), (b) weekly consumption of potatoes (4-5 servings/week), fish (4-5 servings/week), olives, pulses, and nuts (>4 servings/week), and eggs and sweets (1-3 servings/week), and (c) monthly consumption of red meat and meat products (4-5 servings/month) and a moderate wine consumption (1-2 wineglasses/day). They report that the Mediterranean diet encourages an adequate intake of carotenoids, vitamin C, tocopherols, α -linolenic acid (ALA), and several possibly beneficial non-nutrient substances such as polyphenols and anthocyanins. The diet is low in saturated fat (less than about 9% energy), with total fat intake ranging from less than 30% to more than 40% of energy⁽³³⁾. In general, the diet contains a high monounsaturated/saturated fat ratio; moderate alcohol intake; high intakes of fibre, vitamins, folate and natural antioxidants; and low intake of animal protein^(34,35).

Dietary patterns in Mediterranean countries have, however, changed substantially over the last number of years⁽³⁶⁾, including in children^(37,38). For example, Sofi et al.⁽³⁹⁾ have examined the dietary habits of 520 clinically healthy individuals from Florence, Italy and have concluded that, in general, these individuals do not follow a typical Mediterranean diet. The prevalence of obesity in Greece has increased substantially, probably due to Westernization of the diet, increased caloric intake and decreased levels of physical activity⁽³¹⁾, while the prevalence of MI and cardiovascular risk factors other than obesity have also increased⁽⁴⁰⁾. Therefore, it is now more common to think of the

Mediterranean diet as the traditional diet, which was consumed in Mediterranean countries in the 1960s.

Assessment of the Mediterranean dietary patterns - the Mediterranean diet score

The data collection process to assess whole diets can be complex and time-consuming⁽⁴¹⁾. While patterns of food intake in the Mediterranean region are diverse, many attempts have been made to create a score which would reflect the intake of components of the Mediterranean diet. Three main methods have been adopted⁽⁴²⁾:

1. Those based on scoring (positive or negative) of components, e.g. the Mediterranean diet score⁽⁴³⁻⁴⁵⁾
2. Those that add or subtract standardized components⁽⁴⁶⁾
3. Those based on ratios of components⁽⁴⁷⁾

The scoring systems have used somewhere between 7 and 16 components of the diet and have been modified for use in children and adolescents. For example, the Mediterranean Adequacy Index is obtained by dividing the sum of the percentage of total energy from typical Mediterranean food groups by the sum of the percentage of total energy from non-typical Mediterranean food groups⁽⁴⁷⁾. For full details the readers are advised to read the article by Bach et al⁽⁴²⁾. However, the most widely used scores are summarised below.

One of the first scores to be described⁽⁴³⁾ calculated a diet score based on eight component characteristics of the traditional Mediterranean diet: high monounsaturated/saturated fat ratio; moderate ethanol consumption; high consumption of legumes; high consumption of cereals (including bread and potatoes); high consumption of fruits; high consumption of vegetables; low consumption of meat and meat products; and low consumption of milk and dairy products. The sex-specific median was used as the cut-off for each component. In a later population-based prospective study of 22,043 Greek adults⁽⁴⁴⁾, this initial scoring scheme was adapted to include fish intake.

Martinez-Gonzalez et al⁽⁴¹⁾ developed a shorter dietary intake questionnaire which assessed the frequency of consumption for a typical serving of nine foods items thought to represent the cardioprotective elements of the Mediterranean diet. The resulting score ranges from zero to nine points. The dietary items included in the questionnaire include: olive oil (≥ 1 spoon/day); fruit (≥ 1 serving/day); vegetables or salad (≥ 1 serving/day); fruit (≥ 1 serving/day) and vegetables (≥ 1 serving/day); legumes (≥ 2 servings/week); wine (≥ 1 glass/day); meat (< 1 serving/day); white bread (< 1 /day) and rice (< 1 /week) or whole-grain bread (> 5 /week). The benefit of this questionnaire is that it provides a relatively simple means of assessing Mediterranean diet and can reduce data collection time compared to other dietary scores as it is not necessary to calculate the population-

and sex-specific median to determine the value assigned to each of the individual components of the score, thus allowing the score to be quickly calculated and immediate feedback given to participants. The same group has more recently proposed an extension of this score to include 14 items for monitoring adherence to a Mediterranean dietary intervention⁽⁴⁸⁾.

Fung et al⁽⁴⁵⁾ proposed an adaptation of the original Trichopoulou scores^(43,44) for their analysis of the Nurses' Health Study, calling this the alternate Mediterranean diet score, and focusing on a diet higher in plant food consumption, monounsaturated fat and fish, and lower consumption of animal products and saturated fat. Specific differences from the original Trichopoulou scores include excluding potatoes from the vegetable group, separating fruits and nuts into two categories, eliminating a score for dairy products, including wholegrain products only (rather than cereals as a whole), including only red and processed meats (rather than all meats), and specifying the same range of alcohol intake for males and females. Mitrou et al⁽⁴⁹⁾ used both the alternate (aMed) and traditional (tMed) scores in their prospective analysis of Mediterranean diet and all-cause mortality and found similar associations with mortality no matter which score was used.

Despite these findings of a similar association with overall mortality regardless of the Mediterranean diet score used, there is still uncertainty as to whether currently popular and widely used Mediterranean diet scores are appropriate for non-Mediterranean populations. Other scores are in development, including most recently the Mediterranean-Style Dietary Pattern Score (MSDPS), applied to the Framingham Offspring Cohort (7th examination)⁽⁵⁰⁾.

The Mediterranean diet and disease

The Mediterranean diet has been associated with a lower incidence of CHD, but it has also been associated with reduced all-cause mortality, a lower incidence of several types of cancer^(44,51-54), and better self-perceived mental and physical health⁽⁵⁵⁾.

The Mediterranean diet and total mortality

The traditional Mediterranean diet has been associated with a reduction in total mortality in both population based cohort studies^(43,44,51) and in an intervention study⁽⁵⁶⁾ (discussed in CHD section). In a cohort study of Greek elderly people, a one unit increase in Mediterranean diet score was associated with a 17% reduction in overall mortality⁽⁴³⁾. Meanwhile, the HALE project, a cohort study of elderly European men and women (1507 apparently healthy males and 832 females aged 70-90 y), carried out in 11 European countries, reported that adherence to a Mediterranean diet and healthy lifestyle was associated with lower risk of all-cause mortality (HR 0.77, 95% CI 0.67-0.91) after 10 years of follow-up⁽⁵¹⁾.

In another population-based cohort study, involving 22,043 adults in Greece, Trichopoulou et al⁽⁴⁴⁾ investigated the relationship between the Mediterranean diet and overall mortality. Results showed that a higher adherence to a Mediterranean diet was associated with a significant reduction in total mortality after 44 months of follow-up. A two-point increment in Mediterranean Diet score was associated with a 25% reduction in total mortality⁽⁴⁴⁾, and a similar, although weaker, association has been shown recently after 8.5 y (14% reduction in risk per two point increase in score, 95% CI 0.80, 0.93)⁽⁵⁷⁾. Similarly among 74,607 subjects in the EPIC study, a two-unit increase in Mediterranean diet score was associated with an 8% reduction in mortality⁽⁵⁴⁾.

Sofi et al⁽⁵³⁾ have undertaken a meta-analysis of prospective cohort studies which have, in a primary prevention setting, examined the relationship between adherence to a Mediterranean diet and mortality/chronic disease incidence. Using data on >500,000 subjects and >33,000 deaths, they have reported that a two point increase in the adherence score was significantly associated with a reduced risk of mortality (pooled relative risk 0.91, 95% CI 0.89 – 0.94), cardiovascular mortality (0.91, 95% CI 0.87-0.95), incidence of or mortality from cancer (0.94, 95% CI 0.92-0.96), and incidence of Parkinson's disease and Alzheimer's disease (0.87, 95% CI 0.80-0.96). This meta-analysis included the first prospective cohort study to include participants in the USA⁽⁴⁹⁾.

The Mediterranean diet and CHD

Much of the interest in the role of the Mediterranean diet has concentrated on CHD. There have been a number of population-based studies and intervention studies which have examined the relationship between the Mediterranean diet and CHD.

Population-based observational studies

A number of case-control studies^(58,59) and prospective cohort studies^(44,51) have reported associations between increased adherence to the Mediterranean diet and reduced risk of CHD. More recently, Mitrou et al⁽⁴⁹⁾ reported a reduced risk of CVD mortality in those with the highest versus lowest Mediterranean diet score in men (HR 0.78 (95% CI 0.69, 0.87) and women (HR 0.81 (95% CI 0.68, 0.97) from the National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study, which included 214,284 men and 166,012 women aged 50-71 years. Although the association was more pronounced in smokers, it was also present in patients who had never smoked.

1 The prospective cohort studies which have, in a primary prevention setting, examined the
2 relationship between adherence to a Mediterranean diet and CVD incidence have been subjected to
3 meta-analysis⁽⁵³⁾. A two point increase in the adherence score was significantly associated with a
4 reduced risk of cardiovascular mortality (0.91, 95% CI 0.87-0.95) (Figure 3).

6 Since this meta-analysis was published, Fung et al⁽⁶⁰⁾ have published an analysis of the Nurses'
7 Health Study with 20 years of follow-up, where women in the top aMed quintile were at lower risk
8 of both CHD and stroke compared to those in the bottom quintile (RR 0.71; 95% CI, 0.62 to 0.82; P
9 for trend<0.0001 for CHD; RR, 0.87; 95% CI, 0.73 to 1.02; P for trend=0.03 for stroke).
10 Cardiovascular disease mortality was significantly lower among women in the top quintile of the
11 aMed (RR, 0.61; 95% CI, 0.49 to 0.76; P for trend<0.0001).

13 Not only is the Mediterranean diet associated with a decreased incidence of CHD, but it has been
14 reported that a Mediterranean diet is associated with an improved prognosis among those with
15 existing CHD. In a prospective cohort study, but in a secondary prevention setting, Trichopoulou et
16 al⁽⁶¹⁾ examined the relationship between the level of adherence to a Mediterranean diet and survival
17 in 1302 Greek individuals with a diagnosis of CHD (subset of EPIC study population). Mean
18 follow-up was 3.78 years. A Mediterranean diet scale was used to assess compliance with the diet,
19 with a value of zero or one being assigned to each of nine components of the Mediterranean diet. In
20 this study, it was found that a two-unit increase in the score was associated with a 31% lower
21 cardiac mortality. A similar analysis, but in the larger EPIC elderly study of 2671 participants with
22 6.7 y follow-up revealed a similar association (18% overall lower mortality rate (95% CI 7, 27%)
23 for a two-unit increase in score⁽⁶²⁾.

25 *Intervention studies with clinical endpoints*

26 In the GISSI-Prevenzione Study⁽²⁴⁾, a supplement of vitamin E and omega-3 fatty acid was given to
27 survivors of a recent MI. Patients were also given simple advice to increase intake of Mediterranean
28 foods (fish, fruit, raw and cooked vegetables and olive oil). In an analysis adjusted for treatment
29 allocation (therefore in effect corresponding to a cohort analysis), those individuals with a high
30 consumption of Mediterranean foods had a relatively lower chance of premature death, compared to
31 those with a lower intake. All foods (fish, fruit, raw and cooked vegetables and olive oil) appeared
32 to have protective effects⁽²⁴⁾.

34 The Lyon Diet Heart Study reported a significant reduction in major coronary events over a four-
35 year follow-up period⁽⁶³⁾. This study was a prospective, randomised, single-blinded, secondary

1 prevention trial aimed at reducing the risk of cardiovascular deaths by diet modification and
2 recurrent MI in survivors of a first MI. A total of 605 patients were studied (303 control subjects
3 and 302 study patients). Patients in this study were recruited between 1988 and 1992 and less than
4 one third were on lipid lowering drugs⁽⁵⁶⁾.

5
6 Patients in the experimental group were advised to adopt a Mediterranean-type diet. The patients
7 were advised to include more bread, more root vegetables and green vegetables, more fish, less
8 meat (beef, lamb and pork to be replaced with poultry), to have no day without fruit, and to replace
9 butter and cream with a margarine supplied by the researchers. This margarine had a composition
10 similar to olive oil with 15% saturated fatty acids and 48% oleic acid, but had 5.4% 18:1 trans fatty
11 acids and was also slightly higher in linoleic acid (16.4% vs. 8.6%) and more so in ALA. The oils
12 recommended for salads and food preparation were rapeseed and olive oils exclusively. Moderate
13 alcohol consumption, in the form of wine, was allowed with meals. Control subjects did not receive
14 dietary information from the study investigators. Instead, they were expected to follow the dietary
15 advice given to them by their physicians, similar to that of step 1 of the prudent diet of the
16 American Heart Association⁽⁵⁶⁾.

17
18 An interim analysis of this study, after 27 months of follow-up, demonstrated a protective effect of
19 the Mediterranean intervention, with a reduction in the rate of coronary events of 73% and total
20 mortality of 70%⁽⁶⁴⁾, and the study was, therefore, stopped early. The researchers reported that one
21 of the most remarkable differences between the experimental and control groups was plasma ALA
22 concentration, which increased by 68% in the experimental group⁽⁵⁶⁾.

23
24 In terms of dietary change, subjects in the control group averaged 34% of calories (kcal) from fat,
25 12% from saturated fat, 11% from monounsaturated fat, 6% from polyunsaturated fat, and 312
26 mg/day from cholesterol. In contrast, subjects on the Mediterranean-style diet averaged 30% of kcal
27 from fat, 8% from saturated fat, 13% from monounsaturated fat, 5% from polyunsaturated fat, and
28 203 mg/day from cholesterol. Those on the Mediterranean diet consumed less linoleic acid (3.6%
29 vs. 5.3% kcal), and more oleic acid (12.9% vs. 10.8% kcal), ALA (0.84% vs. 0.29% kcal) and
30 dietary fibre. Plasma fatty acid analysis conducted after 52 weeks of follow-up confirmed the
31 dietary fatty acid data. The plasma levels of ALA were significantly associated with composite
32 outcome (CO) 1 (cardiac death and non-fatal MI)⁽⁵⁶⁾.

33
34 The final report of the study showed that longer follow-up (mean follow-up of 46 months) and
35 inclusion of more events in the analyses confirmed the results of the interim analysis⁽⁶³⁾. There were

1 significant reductions in three CO: CO1 (cardiac death and non-fatal MI; Figure 4), CO2 (CO1 plus
2 unstable angina, stroke, heart failure, pulmonary or peripheral embolism), and CO3 (CO2 plus
3 minor events requiring hospital admission), with adjusted risk ratios ranging from 0.28 to 0.53. The
4 reduction in risk in the Lyon Diet Heart Study was not associated with differences in total
5 cholesterol between the control and experimental groups and the survival curves showed a very
6 early separation quite unlike that seen in the statin trials⁽⁶⁵⁾. It was also reported that several years
7 after randomisation, most experimental patients were still closely following the Mediterranean
8 diet⁽⁶³⁾.

9
10 Although the results of the Lyon Diet Heart Study were impressive, there were some
11 methodological limitations to the study. As the study was stopped early, because of significant
12 beneficial effects noted in the original cohort, this may have led to an overestimation of risk
13 reduction. Baseline diet was only assessed in the experimental group, and the diet of the control
14 group was assumed to be comparable. Therefore, it is unclear whether any dietary changes were
15 made by the control group. In addition, dietary data are reported for only 83 (of 303 randomised
16 into the study) and 144 (of 302 randomised into the study) subjects in the control and experimental
17 groups, respectively. With only 30% of the total control cohort and less than 50% of the total
18 experimental group providing dietary data at the conclusion of the study, the diet of the other
19 subjects who completed the study is not known.

20
21 Another intervention study, the Indo-Mediterranean Diet Heart Study, has been published, reporting
22 fewer cardiac endpoints, sudden cardiac deaths and non-fatal MIs in the intervention compared to
23 the control group⁽⁶⁶⁾. However, concern has recently been expressed regarding the reliability of the
24 study⁽⁶⁷⁾, although the paper has not formally been withdrawn.

25
26 Effectively therefore, there is only a single RCT examining the effect of the Mediterranean diet in
27 the secondary prevention of CHD. The American Heart Association has highlighted the need for
28 further research in this area, taking into account the design limitations of the Lyon Diet Heart
29 Study⁽⁶⁸⁾ while Kris-Etherton et al⁽¹⁵⁾ also recognise that the results of this single trial need to be
30 corroborated in both primary and secondary prevention models. Mente et al⁽¹⁸⁾, in a systematic
31 review of all dietary factors and CHD risk, rank the evidence for Mediterranean diet as strong, but
32 do also recommend further evaluation of dietary patterns in cohort studies and randomised trials.

33
34 There are a number of ongoing studies of the Mediterranean diet with CHD endpoints. The
35 PREDIMED study⁽⁶⁹⁾ (recruitment aim n=9,000) is a parallel group randomised trial which is

designed to assess if implementation of a Mediterranean diet will reduce CVD in a primary prevention setting. Eligible patients include males (55-80yr) and females (60-80yr) with either diabetes or at least 3 major cardiovascular risk factors. The primary endpoint is a composite of cardiovascular death, non-fatal MI and non-fatal stroke. There are various secondary outcome measures, including death of any cause, heart failure, cancer, dementia, as well as changes in blood pressure, lipid profile and markers of inflammation. There are two intervention groups and one control group. Both intervention groups are advised to adopt a Mediterranean diet – one group is supplemented with olive oil and the other with nuts, while the control group are given advice to follow a low-fat diet. The rationale for using two types of Mediterranean diet is that the olive oil arm is enriched with MUFA and phenolic antioxidants whereas the nut diet is supplemented with PUFA and ALA. Recruitment started in 2003 and finished in 2006. Follow-up is for a minimum of 4 years so results will become available in 2010-2011. What is lacking are studies in populations (for example, Northern European populations) where compliance may be less good.

Costs of the Mediterranean diet and cost-effectiveness considerations

In a Canadian study of healthy women recruited from Quebec City, Goulet and colleagues⁽⁷⁰⁾ have shown that adherence to the Mediterranean diet does increase the costs related to certain positive components (vegetables, fruits, legumes, nuts, canola/olive oil, whole grains, poultry and fish) but this is balanced by a reduction in costs for other components (red meat, desserts and sweets, and fast food) such that the overall effect is cost-neutral. However, this may not be the case in all settings.

The cost-effectiveness of a Mediterranean diet after MI has also been evaluated, based on data from the Lyon Diet Heart Study, and concludes that the intervention is highly cost-effective and represents an exceptional return on investment⁽⁷¹⁾, while a similar conclusion was drawn by the ATTICA investigators⁽⁷²⁾.

Cardioprotective components of the Mediterranean diet

At this stage it is uncertain which components of the Mediterranean diet are protective against CVD. There is evidence that olive oil has beneficial properties^(25,73) and the diet allows the consumption of large quantities of vegetables, salads and legumes⁽³³⁾. Omega-3 fatty acids are also thought to be important⁽⁶⁸⁾. The evidence for the cardioprotective effect of some of the components of the Mediterranean diet is reviewed below.

Olive Oil

1 In Mediterranean countries, olive oil has traditionally been consumed in large quantities. This has
2 resulted in high levels of dietary fat as a percentage of total calories, with values ranging from 25%
3 to 40% or more⁽⁷⁴⁾. Evidence suggests that olive oil may play a role in the prevention of CHD⁽⁷⁵⁾,
4 most likely due to its high levels of monounsaturated fatty acids (MUFA) and polyphenolic
5 compounds^(31,73). MUFA, found in olive oil and canola oil, are known to have beneficial effects on
6 LDL- and HDL-cholesterol profiles⁽⁷³⁻⁷⁶⁾, and also decrease platelet sensitivity and aggregation, as
7 well as increase fibrinolysis⁽⁷³⁾. The polyphenols found in olive oil may also have antioxidant
8 effects⁽⁷⁷⁾, and monounsaturated fatty acids are not substrates for lipid peroxidation.

10 *Omega-3 fatty acids*

11 Fish is an important source of omega-3 fatty acids, although grains, oils and some nuts are
12 alternative sources. Marine sources provide eicosapentaenoic acid (EPA) and docosahexaenoic acid
13 (DHA). Vegetable sources, including flaxseed, canola (rapeseed) oil, certain nuts and vegetables,
14 provide ALA^(78,79). ALA is a known precursor of long chain omega-3 fatty acids. Consumption of
15 fish and fish oils is known to decrease total cholesterol, serum triglycerides and LDL-cholesterol
16 and may slightly increase HDL-cholesterol⁽⁷⁶⁾.

17
18 A number of studies have examined both fish consumption and omega-3 fatty acid intake in relation
19 to CHD risk.

21 *Studies on fish consumption*

22 Using data from the observational Nurses' Health Study, Hu et al⁽⁸⁰⁾ examined the association
23 between fish and long chain omega-3 fatty acid intake and found that high consumption of fish and
24 omega-3 fatty acids was associated with a lower risk of CHD. In the Diet And Reinfarction Trial
25 (DART), subjects (n>2000, post-MI patients) who were advised to eat oily fish had a 29% reduction
26 in two year all-cause mortality⁽⁸¹⁾. However, in DART-2, where 3114 men with stable angina were
27 advised to eat oily fish or take fish oil supplements and followed up for 3-9 years, there was no
28 effect on all-cause mortality, and a significant increase in cardiac death, this being largely confined
29 to the fish oil supplement group^(82,83). A weakness of this study, however, was a lack of objective
30 markers of dietary compliance, and the authors postulate that compliance with the intervention may
31 have been low.

33 *Studies on omega-3 fatty acid intake*

34 In addition to the DART-2 study described above, two further large intervention trials of fish oil
35 supplementation have been carried out⁽⁷⁹⁾. In the GISSI-Prevenzione trial, over 11,000 patients with

recent MI were given supplements of omega-3 fatty acids, vitamin E, both or no treatment. Total mortality and sudden death were found to be significantly lower in those supplemented with omega-3 fatty acids as soon as three months after treatment commenced^(84,85). The JELIS study, conducted in Japan, in over 18,000 hypercholesterolaemic patients showed that EPA supplementation significantly reduced non-fatal coronary events, but had little effect on cardiac death⁽⁸⁶⁾. This result is in contrast with previous studies which had suggested little effect of fish oils on non-fatal coronary events, but an effect on cardiac death⁽⁸⁷⁾. The lack of effect on cardiac death may not be surprising, as fish intake is already high in Japan, and, therefore, most of the population may already have been above the threshold for an effect of fish oil consumption on cardiac death, and a dose dependent effect has been suggested⁽⁸⁷⁾.

A systematic review of the evidence of the effects of long chain and short chain omega-3 fatty acids had found no strong evidence of a reduced risk of total mortality or combined cardiovascular risk in those taking additional omega-3 fats⁽⁸⁸⁾, but this did not include the JELIS study results. Mente et al⁽¹⁸⁾ in the most recent systematic review looking at dietary factors and CHD, describe the strength of evidence as moderate for marine n-3 fatty acids, and describe the evidence of benefit as observed predominantly in female cohorts and secondary prevention RCTs. A further trial, the Alpha Omega Trial in post-MI patients, is currently ongoing⁽⁸⁹⁾.

The suggested mechanism by which fish oils may reduce risk of cardiac events is through antiarrhythmic effects^(83,87), antithrombotic effects⁽⁷⁸⁾ or possibly enhanced plaque stability⁽⁹⁰⁾. However, it has been suggested that in certain sub-groups of patients fish oils may not be protective and may even increase arrhythmias⁽⁸³⁾. Raitt et al⁽⁹¹⁾ observed an increased risk of recurrent ventricular arrhythmias or fibrillation in patients with implantable defibrillators in response to fish oil, although when this study was combined with two others and a meta-analysis carried out, there was no effect⁽⁹²⁾.

ALA

Dietary ALA intake was associated with reduced risk of fatal CHD after 10 years of follow-up in the Nurses' Health Study⁽⁹³⁾, although by 18 years of follow-up, the observed association was largely confined to sudden cardiac death⁽⁹⁴⁾. The Health Professionals' Follow-up Study, a cohort study of 44,895 men in the United States, also reported an inverse relationship between ALA and CHD risk. In this study, intake of marine omega-3 fatty acids was not inversely related to CHD risk, indicating that the protective effects of ALA may not be the same as those of the marine omega-3 fatty acids⁽⁹⁵⁾.

In the Lyon Diet Heart Study, patients were given margarine high in ALA (containing approximately 5% ALA). At the end of the 52 week follow-up, ALA concentration had increased by 68% in the experimental group⁽⁵⁶⁾. Plasma ALA was the only fatty acid to be significantly associated with an improved prognosis⁽⁶³⁾. The investigators suggest that the protective effect observed in the experimental group was likely to be at least partly due to ALA⁽⁶³⁾.

It has been suggested that ALA may exert an antiarrhythmic effect⁽⁹⁴⁾. However, a systematic review has shown no effect of ALA on cardiovascular risk factors⁽⁹⁶⁾, and it is recognised that more research needs to be done on the potential cardioprotective effects of ALA^(18,78). A further trial, the Alpha Omega Trial using a factorial design to examine the effects of marine n-3 fatty acids versus plant n-3 fatty acids in post-MI patients, is currently ongoing⁽⁸⁹⁾.

Fruit and vegetables

The Mediterranean diet is rich in fruit and vegetables (F&V) and epidemiological evidence, including meta-analyses, tends to support the idea that F&V are protective against CHD⁽⁹⁷⁻⁹⁹⁾. Lock et al⁽¹⁰⁰⁾ estimate that increasing F&V intake to 600g/day could reduce the global burden of CHD by 31%, but RCT evidence examining the effect of increased F&V consumption on cardiovascular endpoints is not currently available. Two studies have shown increased F&V intake to reduce blood pressure^(101,102), whilst another has shown that increasing F&V consumption in hypertensives improves arterial function⁽¹⁰³⁾. In the Lyon Diet Heart Study, vitamin C, a biomarker of F&V consumption, was increased in the intervention group⁽⁶⁴⁾.

Wine

Red wine leads to increased plasma concentrations of antioxidant polyphenols and has beneficial effects on endothelial function⁽²⁰⁾. The *in vitro* inhibition of LDL-cholesterol oxidation by flavonoids, found in red wine, has also been demonstrated⁽¹⁰⁴⁾. Renaud & de Lorgeril⁽¹⁰⁵⁾ state that the French Paradox, the high intake of saturated fat but low CHD mortality seen in France, may be partly explained by a high wine consumption. Using the Lyon Diet Heart Study data, de Lorgeril et al⁽¹⁰⁶⁾ studied the association between alcohol intake and risk of recurrence in survivors of a first MI and found that moderate wine drinking was associated with a significant reduction in cardiovascular complications. These observations have been confirmed by meta-analysis for overall wine consumption⁽¹⁰⁷⁾, although some studies have questioned whether the type of alcohol consumed is important⁽¹⁰⁸⁾. Determining the independent effect of alcohol as opposed to other lifestyle factors in

1 observational studies is difficult⁽¹⁰⁹⁾. The evidence for a benefit of overall alcohol consumption on
2 CHD risk is described as moderate by Mente et al⁽¹⁸⁾.

3
4 The main components of the Mediterranean diet thought to be associated with a reduced risk of
5 CHD have been described above, although there will be other dietary changes, for example
6 increased fibre consumption and reduced red meat consumption, which may also be beneficial.
7 From the results of the Lyon Diet Heart Study, de Lorgeril et al⁽⁶⁴⁾ state that omega-3 fatty acids,
8 oleic acid and antioxidant vitamins are likely to be cardioprotective. However, it is interesting to
9 note that, when Trichopoulou et al⁽⁴⁴⁾ were assessing the associations between Mediterranean diet
10 score and survival (after a median of 44 months of follow-up), there were no strong associations
11 seen for each of the individual dietary components of the Mediterranean diet score, suggesting that
12 it is the overall pattern that is protective. Analysis of the same cohort after 8.5 years has shown that
13 certain components of the Mediterranean diet did contribute more than others – moderate ethanol
14 consumption, low consumption of meat and meat products, high vegetable consumption, high fruit
15 and nut consumption, high MUFA to SFA ratio, and high legume consumption contributed,
16 whereas high cereal consumption, low dairy consumption and high fish consumption did not
17 contribute⁽⁵⁷⁾. The authors suggest a lack of association with cereal and dairy consumption because
18 of the heterogeneity of these food groups, and this has been dealt with in later Mediterranean Diet
19 Scores, and that the lack of association with fish is because fish consumption was low in this
20 population⁽⁵⁷⁾.

21 22 **Mechanism of action**

23 *Mediterranean diet and inflammation*

24 CHD is, in part, an inflammatory disease⁽⁴⁾ and inflammatory mechanisms are known to be
25 important in determining the stability of atherosclerotic plaques⁽¹¹⁰⁾. Plasma levels of some markers
26 of inflammation, including C-reactive protein (CRP) and interleukin (IL)-6 have been shown to
27 predict future cardiovascular risk⁽¹¹⁰⁾. A number of studies have examined associations between the
28 Mediterranean diet and inflammatory markers.

29
30 In the ATTICA Study⁽¹¹¹⁾, those in the highest tertile of Mediterranean Diet score had, on average,
31 20% lower CRP levels, 17% lower IL-6 levels, 15% lower homocysteine levels, 14% lower white
32 blood cell counts and 6% lower fibrinogen levels, compared to those in the lowest tertile. A similar
33 negative association between adherence to the Mediterranean diet and CRP and IL-6 concentrations
34 has recently been shown in MI survivors⁽¹¹²⁾, with a twin study also showing a negative association
35 for IL-6, but not CRP⁽¹¹³⁾.

A randomised trial has assessed the effect of a Mediterranean-style diet on endothelial function and vascular inflammatory markers in patients with metabolic syndrome⁽¹¹⁴⁾. Patients in the intervention group received advice on a Mediterranean-style diet, while those in the control group were given general advice on healthy food choices. After two years of follow-up, patients following the Mediterranean-style diet had significantly reduced serum concentrations of high sensitivity CRP (p=0.01), IL-6 (p=0.04), IL-7 (p=0.04) and IL-18 (p=0.03), as well as decreased insulin resistance (p<0.001). Esposito et al⁽¹¹⁴⁾ concluded that one of the mechanisms responsible for the cardioprotective effect of the Mediterranean diet may be through reduction of a low-grade inflammatory state associated with the metabolic syndrome.

The PREDIMED investigators have looked at the effect of the Mediterranean diet on immune cell activation and inflammation in a subset of their participants (112 older subjects with diabetes or ≥ 3 CVD risk factors)⁽¹¹⁵⁾. Both Mediterranean diet intervention groups (with olive oil or nuts) had decreased IL-6 and sICAM-1 after 3 months, while monocyte expression of CD49d, an adhesion molecule important for leucocyte homing, and CD40, a pro-inflammatory mediator, were also decreased in the two Mediterranean diet groups.

Two studies have recently examined the association between the Mediterranean diet and adiponectin concentrations, because of the proposed anti-inflammatory effect of adiponectin in addition to its effects on insulin resistance. Adherence to the Mediterranean diet was associated with higher adiponectin concentrations in both studies^(116,117). These observations have yet to be confirmed in intervention studies.

Mediterranean diet and endothelial function

Several studies have examined the effects of a Mediterranean-type dietary intervention on intermediate endpoints such as endothelial function. Fuentes et al⁽¹¹⁸⁾ showed an increase in flow-mediated dilatation, suggesting an improvement in endothelial function in hypercholesterolaemic men. This effect is likely to be due to increased antioxidant intake, as Vogel et al⁽¹¹⁹⁾ have examined the postprandial effects of components of the Mediterranean diet on endothelial function. A meal containing olive oil as a fat source reduced brachial artery flow-mediated vasodilation by 31%, but this decrease was reduced by the concomitant administration of vitamins C and E (71%) or balsamic vinegar and salad (65%). Similarly, a meal containing a combination of olive oil rich in antioxidants (green compared to refined) and red wine (compared to white wine) improved flow

mediated dilatation in healthy volunteers, whereas the low antioxidant versions of these foods had no effect⁽¹²⁰⁾.

In an intervention study in metabolic syndrome patients⁽¹¹⁴⁾ described above, endothelial function (defined as a score describing blood pressure and platelet aggregation response to L-arginine infusion) also improved after 2 years in the intervention group ($p < 0.001$).

Mediterranean diet and metabolic syndrome

As described above for inflammation and endothelial function, in a trial of 180 patients with the metabolic syndrome where patients were randomized to a standard diet or a Mediterranean-diet, Esposito et al⁽¹¹⁴⁾ showed that after adoption of a Mediterranean diet for 2 years only 40 of the patients randomized to the Mediterranean diet arm still fulfilled criteria for the metabolic syndrome, compared with 78 patients in the control group ($p < 0.001$). Dietary analysis of this study showed that those following the Mediterranean diet had a greater fibre, PUFA and MUFA and complex carbohydrate intake, a lower ratio of omega-6 to omega-3 fatty acid intake, and lower intakes of energy, saturated fat and cholesterol. Total fruit, vegetable, nut, wholegrain and olive oil consumption was also higher in the intervention group.

The PREDIMED Investigators⁽¹²¹⁾ have undertaken an interim analysis after 1 year on a subset of their participants who were older and at high risk of CVD. At baseline just over 61% fulfilled criteria for metabolic syndrome. They found that the Mediterranean diet supplemented with nuts but not olive oil significantly reduced the prevalence of MetS at 1 year by 13.7%.

Mediterranean diet and diabetes

The SUN (Seguimiento Universidad de Navarra) project is a prospective cohort study ($n = 13,380$) of graduates of the university of Navarra, registered nurses in Spain, and other university graduates. Martinez-Gonzalez et al⁽¹²²⁾ have reported that adherence to a Mediterranean diet is associated with a reduced risk of development of diabetes (incidence rate ratios adjusted for age and sex compared to those with low adherence scores 0.41 (95% CI 0.19-0.87) for those with moderate adherence and 0.17 (95% CI 0.04-0.75) for those with high adherence). One potential mechanism suggested by the authors relates to evidence that extra virgin olive oil may protect against insulin resistance. Patients on Mediterranean diet interventions have reduced plasma glucose^(48,114,123) and HOMA score⁽¹¹⁴⁾.

Mediterranean diet and lipids

1 In the Medi-RIVAGE Study, the effects of either a Mediterranean-type diet or a low-fat diet for 3
2 months on cardiovascular risk factors were evaluated in over 200 French volunteers with moderate
3 risk for CVD⁽¹²⁴⁾. The volunteers were advised to either adopt a Mediterranean-type diet or a low-
4 fat diet, similar to that of the American Heart Association. Neither of the groups complied
5 completely with the diets, but there were changes in clinical and biological markers, including total
6 cholesterol and triglycerides in both intervention groups. The observed lowering in plasma
7 cholesterol indicated a potential 9% reduction in cardiovascular risk in the low-fat diet group
8 compared to 15% in the Mediterranean diet group⁽¹²⁴⁾. Other intervention studies have also
9 demonstrated a beneficial lipid-altering effect^(125,126), including HDL-raising effects^(48,114).

11 *Mediterranean diet and body weight and blood pressure*

12 Intervention studies have demonstrated an effect of the Mediterranean diet on BMI in some^(114,125),
13 but not all⁽⁴⁸⁾ studies. In a study of different weight loss diets, a restricted calorie Mediterranean
14 diet produced a greater weight loss than a low fat, restricted calorie diet, and also had beneficial
15 effects on glycaemic control⁽¹²³⁾.

17 Mediterranean diet interventions have also been shown to reduce blood pressure^(48,114), and
18 adherence to the Mediterranean diet has recently been shown in a longitudinal study to be related to
19 reduced age-related changes in blood pressure⁽¹²⁷⁾.

21 *Antioxidant effects of Mediterranean diet*

22 A number of studies have examined the association between adherence to the Mediterranean diet, as
23 an antioxidant-rich diet, and various biomarkers of oxidative stress. Dai et al⁽¹²⁸⁾ examined the ratio
24 of reduced-to-oxidised glutathione in a twin study, and showed a significant association with
25 Mediterranean diet, which was not confounded by genetic or shared environmental factors.
26 Pitsavos et al⁽¹²⁹⁾ showed an association between Mediterranean diet adherence and both total
27 antioxidant capacity and oxidised LDL cholesterol concentrations in the ATTICA study. These
28 associations from observational studies have been confirmed by an analysis of PREDIMED
29 intervention data after 3 months, where both oxidised LDL levels and malondialdehyde
30 concentrations in mononuclear cells were decreased in the two Mediterranean diet interventions,
31 although effects on serum glutathione peroxidase activity were not observed⁽¹³⁰⁾.

33 **Public health considerations/need for further research**

1 There is, therefore, increasing evidence from epidemiological and intervention studies regarding the
2 benefits of the Mediterranean diet on CHD. However, there are a number of important areas where
3 further research must be carried out.

4
5 *A need for further intervention trials and epidemiological studies?*

6 The results of the Lyon Diet Heart Study⁽⁶³⁾, if replicated in other populations, could provide a
7 substantially enhanced method of reducing the morbidity and mortality associated with CHD. The
8 systematic review carried out by Mente et al⁽¹⁸⁾ calls for further studies investigating dietary
9 patterns, including the Mediterranean dietary pattern, in cohort studies and RCTs, and, ultimately
10 these will have to be tested in the primary and secondary prevention settings.

11
12 It is important to remember, however, that since the Lyon Diet Heart Study was carried out, the
13 pharmacological management of post-MI patients has also changed significantly, with widespread
14 use of statins, ACE inhibitors, beta-blockers and aspirin and it remains unclear whether the impact
15 of dietary change is likely to be maintained in this different pharmacological milieu. A repeat of the
16 Lyon Diet Heart Study, therefore, assumes even greater importance.

17
18 Rimm and Stampfer⁽¹³¹⁾ highlight the difficulties faced by researchers when trying to design
19 randomized trials to study the effects of diet / lifestyle on clinical outcomes and they emphasise the
20 importance of epidemiological investigations and studies which use intermediate endpoints. For
21 observational studies they recommend large studies with repeated comprehensive dietary
22 assessments, coupled where possible with biochemical assays of nutrients, as these will define
23 dietary intakes with greater accuracy, and permit better quantification of intake of nutrients and
24 foods.

25
26 A crucial consideration in observational epidemiology is how one separates the effects of diet from
27 other lifestyle choices such as exercise, social class, and cultural differences and it is not certain that
28 adjustment for known confounders really does take account of these interactions. For example, it
29 has been suggested that the effect of the Mediterranean diet may be explained by potential
30 geographic, social, and other cultural differences among target populations⁽⁶⁸⁾, including attitudes to
31 food and to the diet-health link⁽¹³²⁾. The ultimate proof of causality needs to come from randomised
32 controlled trials, and the possibility of residual confounding constantly acknowledged in
33 observational epidemiological studies. Recent studies have looked at overall lifestyle patterns,
34 rather than just dietary patterns. These include some method of assessment of diet quality,
35 smoking, alcohol consumption, physical activity, and BMI, and have demonstrated strong

associations with cardiovascular, cancer and total mortality⁽¹³³⁻¹³⁷⁾, and, therefore, the development of a lifestyle score which encompasses adherence to the Mediterranean diet may be a useful tool in future epidemiological studies.

Mediterranean diet pattern and non-Mediterranean populations

Most of the observational studies and one intervention study with clinical endpoints have been carried out in Mediterranean/European populations, although Mitrou et al⁽⁴⁹⁾ did confirm the association with mortality in an American population. It has been suggested that the Mediterranean diet may be difficult to adopt in other populations due to differences in cultural and environmental conditions⁽³³⁾, while Bemelmans et al⁽¹³⁸⁾ have suggested that the Lyon Diet Heart Study may be difficult to replicate in Northern European populations. De Lorgeril et al⁽⁶³⁾ recognise that new dietary habits need to be financially and gastronomically acceptable and practically feasible for patients (and their relatives).

A number of studies have sought to determine if the Mediterranean diet is transferable to other populations. A study in Germany investigated if it was theoretically possible to implement some characteristics of the Mediterranean diet into the German food pattern. This was done by comparing the food consumption data of four Mediterranean countries with that of Germany. Results showed that Germans ate fewer vegetables, cereals and pulses and more animal products, but that availability of food was such that components of the Mediterranean diet could be incorporated into German food patterns⁽¹³⁹⁾.

Two studies have examined a Mediterranean diet intervention in clinical populations. Logan et al⁽¹⁴⁰⁾ showed that dietary advice to adopt a Mediterranean diet in MI patients led to significant increases in Mediterranean Diet Score of about 3 units at both 6 months and 12 months. Three different methods of delivering dietary advice were tested, including behavioural counselling, but dietary change was achieved regardless of the method of advice delivery used. McKellar et al⁽¹⁴¹⁾ achieved significant increases in total fruit, vegetable and legume consumption and an improvement in the MUFA:SFA intake ratio in rheumatoid arthritis patients in Glasgow assigned to a Mediterranean diet intervention.

Changing dietary patterns worldwide

These interventions occur against a background of globalization and convergence of dietary patterns towards a typical Western diet, and this is not just a problem for Mediterranean countries, as outlined above⁽¹⁴²⁾. Less developed countries are tending to adopt more energy-dense diets rich in

1 animal products and fast-food consumption^(142,143). Public health policy options range from
2 measures to raise awareness of the health benefits of the Mediterranean diet, or other healthy dietary
3 patterns, through changing relative food prices in favour of such diets, to taxing people who do not
4 follow such diets and are, therefore, more prone to develop chronic disease with associated
5 healthcare costs⁽¹⁴³⁾.

6 7 *Factors determining adherence to a Mediterranean diet*

8 At present, little work has been carried out to determine what factors are associated with adherence
9 to a Mediterranean diet, and how public health messages can best be promoted. The PREDIMED
10 Investigators⁽⁶⁹⁾ have shown that a 1-year behavioural intervention, comprising both group and
11 individual sessions by dietitians, in conjunction with the provision of certain key foods of the
12 Mediterranean diet, did result in improved dietary habits of the participants, who were at high risk
13 of CVD, and a similar effect of dietary advice has been shown for CHD patients⁽¹⁴⁰⁾. Whether such
14 interventions would be effective for the general population remains to be determined, although
15 Sanchez-Villegas et al⁽¹⁴⁴⁾ have shown among university students that women were more compliant
16 with the Mediterranean diet pattern than men, that younger participants (both male and female)
17 were less likely to comply and that those who were more physically active were more likely to
18 follow a Mediterranean diet pattern.

19 20 *Current dietetic advice for secondary prevention of CHD*

21 UK dietetic guidelines on the dietary advice that should be given in the secondary prevention of
22 CVD⁽¹⁴⁵⁾ state that every person who has CHD should be advised to reduce saturated fats and
23 replace these with unsaturated fats, and people who have had a MI should be advised to increase
24 marine n-3 fat intake (an update from the British Dietetic Association confirms this as a
25 recommendation to consume at least 2 large servings of oily fish a week), and also given
26 'Mediterranean' dietary advice (advice to increase omega-3 fats, F&V and fresh foods and to
27 reduce saturated fats and processed foods). These recommendations largely concur with those
28 given by the National Institute for Health and Clinical Excellence⁽¹⁴⁶⁾ for cardiovascular risk
29 assessment and the modification of blood lipids for the primary and secondary prevention of CVD.

30 31 **Conclusion**

32 It is clear that diet is associated with the development of CHD. The incidence of CHD is lower in
33 Southern European countries than Northern European countries and it is thought that this may, at
34 least partly, be due to diet. Numerous studies have shown that the Mediterranean diet appears to
35 protect against CHD, and this has been confirmed by meta-analysis. However, it is uncertain

1 whether the benefits of the Mediterranean diet are transferable to other non-Mediterranean
2 populations, and whether the effects of the Mediterranean diet, as demonstrated in the Lyon Diet
3 Heart Study, will still be feasible in light of the changes in pharmacological therapy seen in CHD
4 patients since the study was conducted. Further work needs to be carried out to answer this
5 question, and if such an effect is confirmed, then the best methods to effectively deliver this public
6 health message worldwide considered.

7

8 Conflicts of interest: None declared

9 Contribution of each author: PPMcK, KL and JW discussed review content and produced the initial
10 manuscript draft, and MMcK and ISY critically revised this initial draft. All authors read and
11 approved the final version of the manuscript.

12

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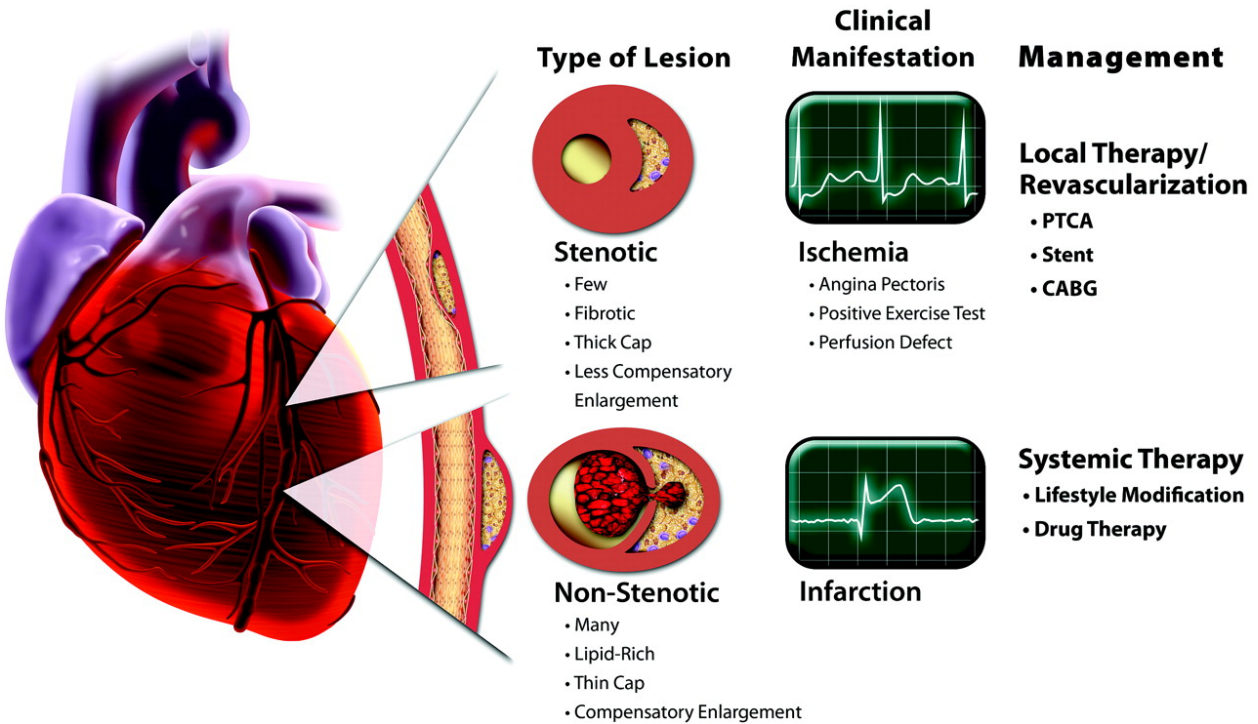
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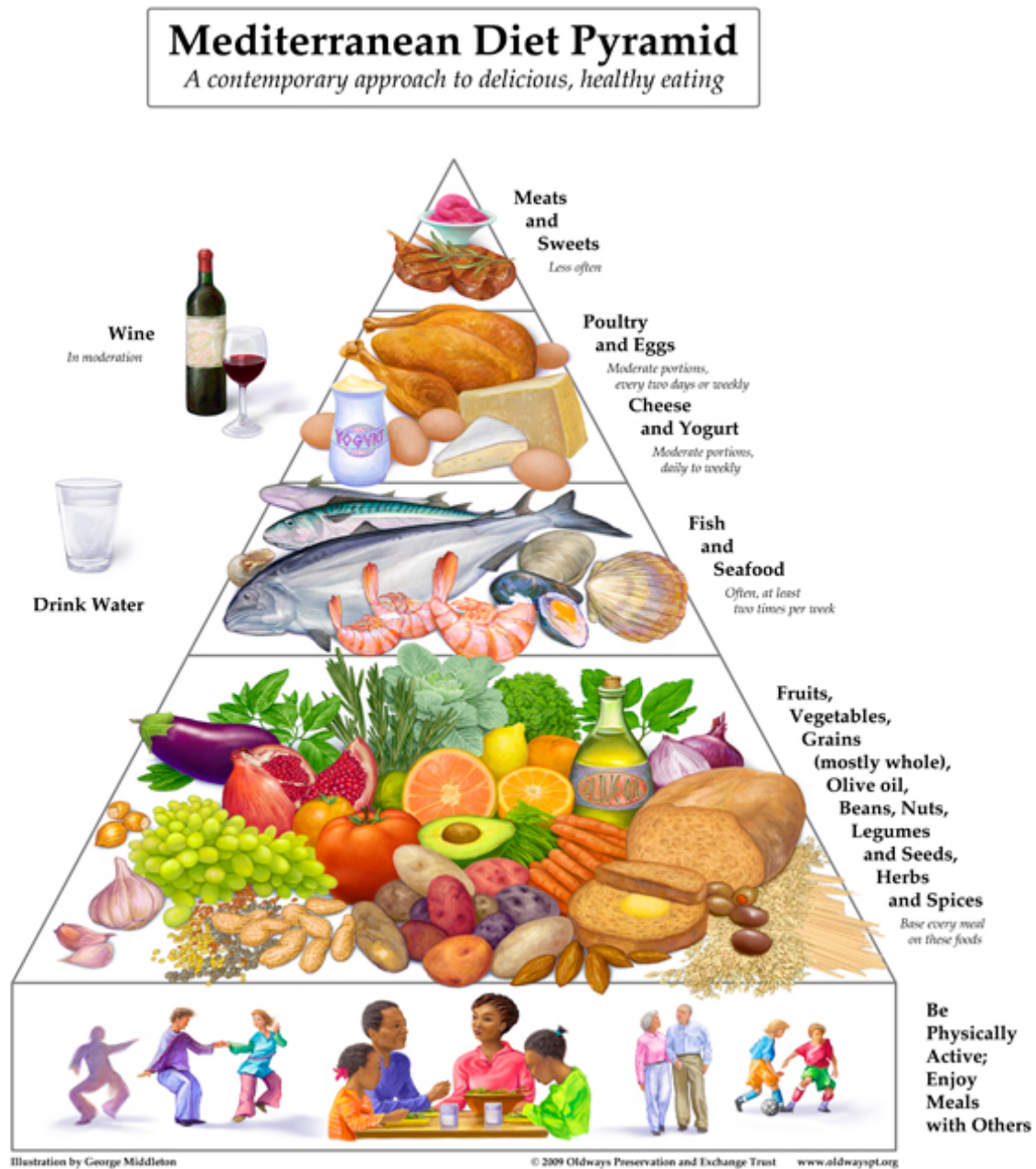
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Figure 1. Simplified schema of diversity of lesions in human coronary atherosclerosis.



This schematic depicts 2 morphological extremes of coronary atherosclerotic plaques. Stenotic lesions tend to have smaller lipid cores, more fibrosis, and calcification; thick fibrous caps; and less compensatory enlargement (positive remodeling). Nonstenotic lesions generally outnumber stenotic plaques and tend to have large lipid cores and thin, fibrous caps susceptible to rupture and thrombosis. They often undergo substantial compensatory enlargement that leads to underestimation of lesion size by angiography. Nonstenotic plaques may cause no symptoms for many years but when disrupted can provoke episode of unstable angina or MI. Enlarged segments of schematic show longitudinal section (left) and cross section (right). Many coronary atherosclerotic lesions may lie between these 2 extremes, produce mixed clinical manifestations, and require multipronged management. PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

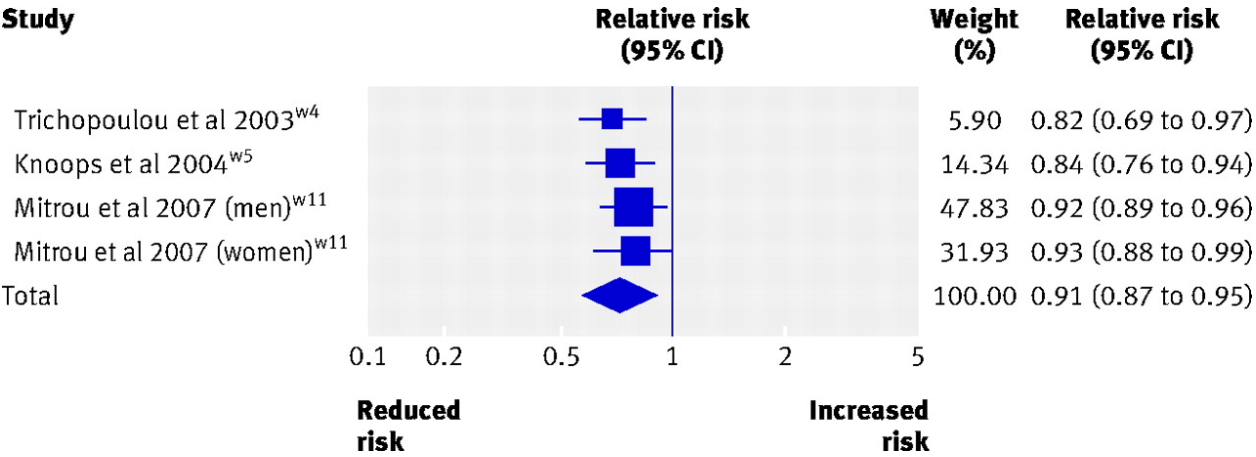
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1
 2 Figure 2. Key features of the Mediterranean Diet expressed as a Mediterranean Diet Pyramid
 3 (Reproduced with permission from: © 2009 Oldways Preservation & Exchange Trust;
 4 www.oldwayspt.org)
 5

1 Figure 3 Risk of mortality from cardiovascular diseases associated with two point increase in
2 adherence score for Mediterranean diet.

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7 Squares represent effect size; extended lines show 95% confidence intervals; diamond represents
8 total effect size. Reproduced from⁽⁵³⁾ with permission from BMJ Publishing Group Ltd.

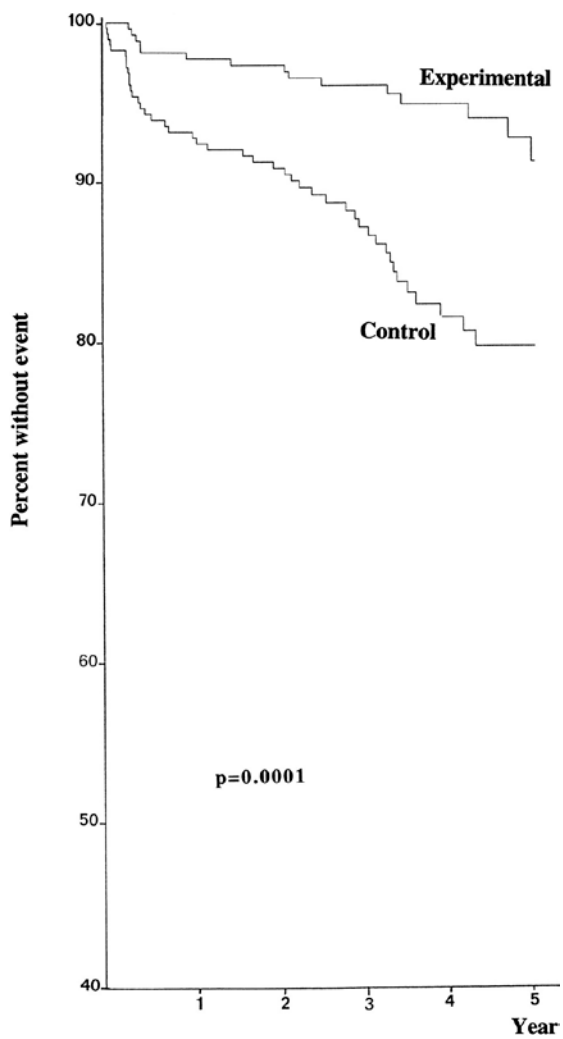
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1 Figure 4 Cumulative survival without nonfatal myocardial infarction (CO 1) among experimental
2 (Mediterranean group) patients and control subjects
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